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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/931,375	08/17/2001	Matthew L. Warman	38464-0004	1602

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EXAMINER	
SEHARASEYON, JEGATHEESAN	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 03/18/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/931,375	WARMAN ET AL.	
	Examiner	Art Unit	
	Jegatheesan Seharaseyon	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 November 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8 and 30-36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8 and 30-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *13 March 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

'Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/29/02, 10/11/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election without traverse of claims 8, 9 and 30-36 (group IV) in the reply filed on 11/20/2003, 6/28/2004, 7/19/2004 and 11/5/2004 is acknowledged. Claims 1-7 and 10-29 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a non elected group, there being no allowable generic or linking claim.

Priority

2. Applicants are entitled to the priority date of instant Application filing date 08/17/2001. In order to obtain a earlier filing date the later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994). Specifically the disclosure with respect to treating osteoporosis or BSMR effector molecules are not recited in the previous Applications.

Information Disclosure Statement

3. The Office acknowledges the receipt of IDS submitted on 3/29/2002 and 10/11/2002.

Drawings

4. The drawings submitted on 3/15/2002 is acknowledged.

Specification

5. The use of the trademarks such as QUIKChage, GeneChips and TOPflash etc. has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

6. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). **Specifically, the sequences disclosed in Figures 2, 3, 5, 6 and 13 are not accompanied by the required reference to the relevant sequence identifiers. Additionally, the specification discloses primer sequences at pages 55-56 and 59 that are not accompanied by the required reference to the relevant sequence identifiers.** This application fails to comply with the requirements of 37 CFR 1.821 through 1.825. Applicant must comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825).

Claim Objections

7. Claim 8 is objected to for failing to adhere to the requirements of the sequence rules. Applicant must append SEQ ID Nos. to all mentions of specific sequences in the specification and the claims. See 37 CFR § 1.821(d). Applicant is required to recite the specific SEQ ID No in the claims instead of referring to the Figures.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 8, 9 and 30-36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

8a. Claim 8 is indefinite in the recitation of the phrase "capable of" is ambiguous and not clear and is a relative term which renders the claim indefinite. The term "capable of" is not defined by the claim and the specification does not provide a standard for ascertaining as such.

8b. Claim 8 that recites stringency is relative, and the art does not recognize a single set of conditions as stringent. The specification also does not provide an unambiguous definition for the term. In the absence of a recitation of clear hybridization conditions (e.g., "hybridizes at wash conditions consisting of **A** X SSC and **B** % SDS at **C**°C"), the claims fail to define the metes and bounds of the varying structures of polynucleotides recited in the claimed methods.

8c. Claims 9 and 30 are rejected as vague and indefinite for reciting the abbreviated terms "dkk protein" and "BSMR protein". The full meaning of an acronym should be spelled out at its first use in any claim. Claims 31-36 are rejected insofar as they depend on claim 30.

8d. Claim 35 recites the limitation "a second morphogenetic protein" in line 2. There is insufficient antecedent basis for this limitation in the claim. Also if this morphogenetic protein is administered prior to step (b) it is unclear how this will be the second protein.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

9a. Claims 8, 30 and 31 are rejected under 35 U.S.C. 102(e) as being anticipated by Carulli et al. (U. S. Patent NO. 6, 780, 609).

The instant invention is directed to polynucleotides associated with a method of regulating bone strength and mineralization.

Carulli et al. (U. S. Patent NO. 6, 780, 609) describe a protein Zmax1 or HBM (SEQ ID NO: 3). This Zmax1 gene is shown as SEQ ID NO: 1 (column 10, lines 50-55).

The specification of this reference also teaches that this gene is involved in the regulation of bone strength and mineralization (columns 4-11). Carulli et al. teach that ligands such as ApoE bind to Zmax1 or HBM and are useful in the regulation (column 84, line 55 to column 85, line 8). Thus, it is termed the "bone strength and mineralization" ("BSMR") gene by the Applicant (see page 6, specification). The polynucleotide sequence described by Carulli et al. would also hybridize to the nucleotide sequence of the instant invention. The reference also teaches the regulation of Zmax1 or HBM gene in TE85 osteosarcoma cell and osteoblasts (column 78-79 and Table 5). Thus meeting the limitations of claim 8. The reference also teaches diagnosis and treating osteoporosis with the instant protein (column 75 lines 30-50 and column 84, lines 20-28). Zmax1 and HBM interact with several proteins, such as ApoE (ligand effectors). Molecules that inhibit the interaction between Zmax1 or HBM and ApoE or another binding partner are expected to alter bone development and mineralization. Such inhibitors may be useful as drugs in the treatment of osteoporosis, osteopetrosis, or other diseases of bone mineralization. Such inhibitors may be low molecular weight compounds, proteins or other types of molecules (column 84, lines 54-61). The reference teaches that once the matrix synthesis begins, osteoblast marker genes are activated in a clear temporal sequence: alkaline phoshatase is induced at early times while bone sialoprotien and osteocalcin appear later in the differentiation process. This temporal sequence of gene expression is useful in monitoring the maturation and mineralization process (column 68, lines 20-30). Since it is an inherent property associated with bone formation it is expected to increase with treatment. Therefore

meeting the limitation of claim 30. In addition, interaction with ApoE meets the limitation of claim 31. Therefore, claims 8, 30 and 31 are rejected under 35 U.S.C. 102(e) as being anticipated by Carulli et al. (U. S. Patent NO. 6, 780, 609).

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10a. Claims 31 and 32 is rejected under 35 U.S.C. 103(a) as being unpatentable over Carulli et al. (U. S. Patent NO. 6, 780, 609) in view of Pinson et al. (2000).

Claims of this invention are drawn to BSMR effector WNT.

Carulli et al. (9a) disclose a low density lipoprotein receptor (LDLR)-related protein (LRP) designated as LRP5 and Zmax1 or HBM respectively. This protein is

described as BSMR that is involved in bone strength and mineralization in the instant invention. They also describe that ApoE (effector) binding to BSMR protein. This in turn modulates the BSMR regulatory system. However, Carulli et al do not disclose modulation of BSMR by WNT protein another effector protein. Pinson et al. (2000) present evidence that a new member of the low-density lipoprotein (LDL)-receptor-related protein family, LRP6, is critical for WNT signaling in mice (page 535). It is claimed that LRP6 is required for efficient signaling by several Wnt signals in mammals (page 537). Specific developmental defects were observed in both LRP6 and WNT mutants (page 535 and 536).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use BSMR protein to modulate bone strength and mineralization as described by Kim et al. or Carulli et al. using WNT proteins because Pinson et al. disclose that LRP6 is critical for signaling WNT. One of ordinary skill in the art would have been motivated to modulate BSMR (LRP5 or Zmax1) using WNT signaling in order to regulate bone strength and mineralization. In addition, one of ordinary skill in the art would have been also been motivated because Pinson et al. describe the signal transduction of LRP6/WT (page 537). Therefore, the instant invention is *prima facie* obvious over Kim et al. (1998, Ref A17 on 1449) or Carulli et al. (U. S. Patent NO. 6, 780, 609) in view of Pinson et al. (2000).

10b. Claims 33 and 34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Carulli et al. (U. S. Patent NO. 6, 780, 609) in view of Oppermann et al. (U. S. Patent NO. 5, 652, 337).

The instant invention is drawn to targeting the BSMR effector to bone producing regions to treat osteoporosis.

Carulli et al. (U. S. Patent NO. 6, 780, 609) disclose a low density lipoprotein receptor (LDLR)-related protein designated as Zmax1 or HBM respectively. This protein is described as BSMR that is involved in bone strength and mineralization in the instant invention. They also describe that ApoE binds to BSMR protein. This in turn modulates the BSMR regulatory system. Carulli et al. also disclose that molecules that inhibit the interaction between Zmax1 or HBM and ApoE or another binding partner are expected to alter bone development and mineralization. It is disclosed that such inhibitors may be useful as drugs in the treatment of osteopetrosis, or other diseases of bone mineralization. Such inhibitors may be low molecular weight compounds, proteins or other types of molecules (column 84, lines 54-61). However, Carulli et al do not disclose compounds that are capable of targeting the BSMR effector to bone producing regions.

Oppermann et al. (U. S. Patent NO. 5, 652, 337) disclose compounds that are capable of targeting BSMR effector to the region of bone remodeling (column 15, lines 38-42). For example, tetracycline and diphosphonates (bisphosphonates) are known to bind to bone mineral, particularly at zones of bone remodeling, when they are provided systemically in a mammal. Accordingly, these molecules may be included as useful agents for targeting OP-3 (a morphogen) to bone tissue. Alternatively, an antibody or

other binding protein that interacts specifically with a surface molecule on the desired target tissue cells also may be used (column 15, lines 38-47).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to target BSMR effector molecules to regions of bone regeneration or remodeling to modulate bone strength and mineralization as described by Carulli et al. using tetracycline and diphosphonates (bisphosphonates) that are known to bind to bone mineral because Oppermann et al. disclose that tetracycline and diphosphonates (bisphosphonates) are known to bind to bone mineral, particularly at zones of bone remodeling, when they are provided systemically in a mammal. One of ordinary skill in the art would have been motivated to modulate BSMR (Zmax1 or HBM) using a BSMR effector such as Apo E that is targeted to bone producing or remodeling region by compounds such as tetracycline and diphosphonates (bisphosphonates) in order to regulate bone strength and mineralization to treat osteoporosis. Therefore, the instant invention is *prima facie* obvious over Carulli et al. (U. S. Patent NO. 6, 780, 609) in view of Oppermann et al. (U. S. Patent NO. 5, 652, 337).

10c. Claims 30, 35 and 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Carulli et al. (U. S. Patent NO. 6, 780, 609) in view of Wang et al. (U. S. Patent NO. 6, 245, 889) and Hughes et al (1995).

The instant invention is drawn to treating osteoporosis by providing BSMR effector and a second morphogenetic protein.

Carulli et al. (U. S. Patent NO. 6, 780, 609) disclose a low density lipoprotein receptor (LDLR)-related protein designated as Zmax1 or HBM respectively. This protein is described as BSMR that is involved in bone strength and mineralization in the instant invention. They also describe that ApoE binds to BSMR protein. This in turn modulates the BSMR regulatory system. Carulli et al. also disclose that molecules that inhibit the interaction between Zmax1 or HBM and ApoE or another binding partner are expected to alter bone development and mineralization. It is disclosed that such inhibitors may be useful as drugs in the treatment of osteopetrosis, or other diseases of bone mineralization. Such inhibitors may be low molecular weight compounds, proteins or other types of molecules (column 84, lines 54-61). Alteration of the level of functional Zmax1 protein or HBM protein affects the level of bone mineralization. By manipulating levels of functional Zmax1 protein or HBM protein, it is possible to affect bone development and to increase or decrease levels of bone mineralization. For example, it may be useful to increase bone mineralization in patients with osteoporosis. Alternatively, it may be useful to decrease bone mineralization in patients with osteopetrosis or Paget's disease. Alteration of Zmax1 levels or HBM levels can also be used as a research tool. (column 83, line 60 to column line 2). However, Carulli et al do not disclose the addition of second morphogenetic protein along with the BSMR effector to bone producing regions.

Wang et al. (U. S. Patent NO. 6, 245, 889) disclose the use of BMP-2 and BMP-4 protein may be combined with other agents beneficial to the treatment of the bone and/or cartilage defect, wound, or tissue in question (column 6, lines 65 to column 7,

lines 42). These agents include various growth factors such as epidermal growth factor (EGF), platelet derived growth factor (PDGF), transforming growth factors (TGF-α and TGF-β), and insulin-like growth factor (IGF) (column 7, lines 2-5). These agents may provide an environment to attract bone-forming cells, stimulate growth of bone-forming cells or induce differentiation of progenitors of bone forming cells (column 6, lines 20-23). Wang et al. teach that for bone and/or cartilage formation, the composition would include a matrix capable of delivering BMP-2, BMP-4 or other BMP proteins to the site of bone and/or cartilage damage (column 7, lines 35-38). It also teaches that BMP-2 may be used individually in a pharmaceutical composition or in combination with BMP-4 and/or one or more of the other BMP proteins (column 7, lines 14-18). Hughes et al. (1995) disclose that the effect of BMPs on nodule formation was seen after only 24hours of exposure to BMPs. It also teaches that continuous or 24-h exposure to BMP-2 or BMP-4 increased the number of postmitotic ALP-positive cells in log phase culture (abstract).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to administer another bone morphogenic protein (BMP) target to regions of bone regeneration or remodeling to modulate bone strength and mineralization as described by Wang et al. using a bone morphogentic protein such as BMP-2 administering BMP-2 at least 24 hrs prior administering the BSMR effector as taught by Hughes et al to increase bone formation because Carulli et al et al. disclose manipulating the levels of functional Zmax1 protein or HBM protein, it is possible to affect bone development and to increase or decrease levels of bone mineralization,

particularly at zones of bone remodeling, when they are provided systemically in a mammal. One of ordinary skill in the art would have been motivated to treat osteoporosis by administering BMP-2 protein 24 hrs prior to providing BSMR effector that is targeted to bone producing or remodeling region in order to regulate bone strength and mineralization to treat osteoporosis. Further, Hughes teaches that BMP-2 or BMP-4 increased the number of postmitotic ALP-positive cells. Therefore, the instant invention is *prima facie* obvious over Carulli et al. (U. S. Patent NO. 6, 780, 609) in view of Wang et al. (U. S. Patent NO. 6, 245, 889) and Hughes et al (1995).

11. No claims are allowable.

Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jegatheesan Seharaseyon whose telephone number is 571-272-0892. The examiner can normally be reached on M-F: 8:30-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on 571-272-0961. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

JS 2/05

JANET ANDRES
PRIMARY EXAMINER